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<b>(21) International Application Number:</b> PCT/GB97/01009 <b>(22) International Filing Date:</b> 9 April 1997 (09.04.97) <b>(30) Priority Data:</b> 9607399.4 10 April 1996 (10.04.96) GB <b>(71) Applicant (for all designated States except US):</b> BESPAC PLC [GB/GB]; Bergen Way, North Lynn Industrial Estate, King's Lynn, Norfolk PE30 2JJ (GB). <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only):</b> BARNES, Paul [GB/GB]; 15 Graham Drive, Fair Green, Middleton, King's Lynn, Norfolk, PE32 1RL (GB). <b>(74) Agent:</b> BOULT WADE TENNANT; 27 Furnival Street, London EC4A 1PQ (GB).		<b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> A METHOD OF CLEANING OR PURIFYING ELASTOMERS AND ELASTOMERIC ARTICLES WHICH ARE INTENDED FOR MEDICAL OR PHARMACEUTICAL USE		
<b>(57) Abstract</b>  A method of cleaning or purifying elastomers and elastomeric articles which are intended for medical or pharmaceutical use which method comprises firstly performing a solvent extraction process on the elastomer or elastomeric article using a solvent in a non-supercritical state to substantially remove impurities therefrom and thereafter subjecting the elastomer or elastomeric article to a further solvent extraction step using a supercritical fluid or a mixture of supercritical fluids in order to remove or substantially reduce the concentration of the residue of extracting solvent remaining in the elastomer or elastomeric article after the first solvent extraction process.		

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**A METHOD OF CLEANING OR PURIFYING ELASTOMERS AND  
ELASTOMERIC ARTICLES WHICH ARE INTENDED FOR MEDICAL OR  
PHARMACEUTICAL USE**

5           This invention relates to a method of cleaning or  
purifying elastomers and elastomeric articles which in  
particular are intended for medical or pharmaceutical  
uses but also for cleaning or purifying elastomers and  
elastomeric articles for any use in which impurities  
10       in the elastomer might cause problems through leaching  
or extraction into the adjacent media.

          Pressurised metered dose inhalers [MDIs] have  
been available over the last thirty years for the  
administration of medicaments or drugs, primarily to  
15       the lungs, for the treatment of asthma and other  
airway diseases. Additionally, they have been used  
for the administration of drugs to the lung for  
systemic absorption, for administration to the oral  
cavity and for administration into the nose. All of  
20       these pressurised inhalers utilise aerosol valves that  
meter individual doses. These metering valves are  
constructed of a mixture of metal and/or plastic parts  
and elastomeric rubbers. Various types of elastomeric  
rubber are used in these valves and newer types are  
25       being continually developed to ensure compatibility  
with the various aerosol propellants, to provide  
compatibility with and stability of the drug  
formulation and to ensure that the valve continues to  
perform to specification over the several years of  
30       storage required of a pharmaceutical product. One  
consequence of this protracted storage of aerosol  
packs in which the propellants are in intimate contact  
with the metering valve is that materials are leached  
or extracted from the elastomeric rubbers into the  
35       drug formulation. These materials which may be

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extracted from the elastomeric rubbers are a mixture of the chemical ingredients originally used to make the rubber and also new chemicals produced during the vulcanisation of the rubber. These are undesirable in the finished rubber component as they may cause instability of the formulation and/or degradation of the drug substance and therefore loss of potency, or they may impart objectionable tastes or odours to the product and could in extreme cases cause allergic or toxic reactions.

Both the pharmaceutical manufacturers and the valve manufacturers have been aware of the above problems associated with the use of elastomeric rubber compounds and various approaches have been employed to reduce the extractable chemical materials contained in the rubbers. The main approaches have been to formulate rubbers that will provide a lower level of extractable chemical materials or to pre-extract the rubbers before assembly into the metering valve. Because the final intended use of the product is for administration of drugs, the choice of extraction solvent which can be used is very limited for safety and toxicity reasons as there will remain in the rubber after solvent extraction a residue of this solvent which will be extracted into the propellant system. For this reason the most common extraction solvent used to pre-extract rubbers is the chlorofluorocarbon Trichlorofluoromethane [ $\text{CCl}_3\text{F}$ ] which is included as part of the propellant system in a number of MDIs. Trichlorofluoromethane has a boiling point of  $23.8^\circ\text{C}$  and is often called Propellant 11 which is abbreviated to P11. Due to its boiling point the liquid can generally be used at ambient temperatures.

This pre-extraction has been carried out by a

variety of methods ranging from soaking the rubbers in P11 with or without stirring, pumping the P11 through a bed of the rubber components to sophisticated custom-designed extraction apparatus where the material extracted from the rubber is continually removed and the rubber continually provided with a stream of pure P11. These methods generally take several days to achieve extraction although extraction is not complete. The processes are intended to reduce the levels of available extractable chemical materials and it is appreciated that they will not be completely eliminated.

More recently the process known as super critical fluid extraction, SCF extraction, has been developed as a general method of extraction for a variety of materials either to remove impurities or to isolate particularly desired chemical compounds.

In WO93/12161 there is described and claimed a method for cleaning elastomeric articles, in particular components for MDIs comprising extracting phthalates and/or polynuclear aromatic hydrocarbons (PAHs) from the articles by contacting the articles with a supercritical fluid. However, a disadvantage of the use of SCFs is that the choice of SCFs which can be used is limited by pressure and temperature considerations as well as toxicity characteristics because residues of the SCF could remain in the rubber after SCF treatment. Thus for practical purposes SCF extraction is mainly limited to the use of carbon dioxide (CO<sub>2</sub>) and probably a small number of other chemicals such as nitrous oxide (N<sub>2</sub>O).

Likewise, traditional rubber extraction solvents have also been limited by toxicity consideration in view of the residual solvent remaining in the rubber after extraction, and for practical purposes the

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choice has usually been between P11, ethanol, ethanol/water mixture and water and a small number of other possibilities.

5        However, it would be useful if it were possible to use other solvents which, although prevented by toxicity considerations from use in hitherto known rubber extraction procedures may have particularly favourable solvent properties for certain of the impurities occurring in the rubbers.

10        According to the present invention there is provided a method of cleaning or purifying elastomers and elastomeric articles which are intended for medical or pharmaceutical use which method comprises firstly performing a solvent extraction process on the  
15        elastomer or elastomeric article using a solvent in a non-supercritical state to substantially remove impurities therefrom and thereafter subjecting the elastomer or elastomeric article to a further solvent extraction step using a supercritical fluid or a  
20        mixture of supercritical fluids in order to remove or substantially reduce the concentration of the residue of extracting solvent remaining in the elastomer or elastomeric article after the first solvent extraction process.

25        It should be understood that the supercritical fluid used in the present invention is not itself employed to remove impurities in the elastomer but rather to remove or substantially reduce the residue of extracting solvent which has been used previously  
30        to remove these impurities. Thus it will be seen that the present invention *inter alia* enables the use for the initial extraction of impurities of extracting solvents would not meet the appropriate toxicity requirements if they left significant residues in the  
35        rubber after treatment, and if these residues were not

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subsequently removed as in the present invention. Thus, for example, in addition to the conventional extracting solvents of which examples are referred to above, acetone could be used in the method of the present invention as an extracting solvent in the first extraction stage.

The primary characteristics of the SCFs used in the method of the present invention are firstly that they should be safe for use with humans, secondly that they should have a sufficiently low critical temperature, ideally less than 100°C, for practical considerations, and thirdly they should also be good extractants for the solvent or solvents used in the first stages of the method but not necessarily for the original impurities in the rubber which will of course have been already substantially extracted by the solvent used in the first stage of the method.

The actual practical procedures and apparatus for performing the method of the present invention are conventional, the first stage of the method being substantially as has been practised hitherto in conventional extraction-purification procedures for elastomers intended for medical and pharmaceutical use, whilst the second stage of the method employs procedures and apparatus which are conventional in the handling of supercritical fluid extractions, the selection of appropriate conditions, temperatures, pressures and timing of treatment being within the skill of the art.

Following are three outline examples of the method of the present invention.

#### Example 1

An elastomeric rubber component for an MDI is extracted by soaking in P11 for 3 days. The P11 is

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then drained away and the rubber components allowed to air dry. The residual and variable amount of P11 remaining in the extracted rubber is reduced by SCF extraction using Nitrous Oxide for 4 hours.

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#### Example 2

Elastomeric rubber components for MDIs are extracted using ethanol for 48 hours. After this period the liquid ethanol is drained off and more of the ethanol is removed from the rubbers by air drying *in situ*. Following this the residual ethanol in the rubbers is further reduced by SCF extraction using Carbon Dioxide at 50°C for 4 hours.

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#### Example 3

Rubber components for MDIs are extracted by reflux with acetone at its boiling point of 56.5°C for 24 hours. The acetone containing the extractables is drained away and the rubber components oven dried at 60°C for 6 hours. Residual acetone in the components is removed using SCF extraction with Carbon Dioxide.

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## CLAIMS:

1. A method of cleaning or purifying elastomers and elastomeric articles which are intended for  
5 medical or pharmaceutical use which method comprises firstly performing a solvent extraction process on the elastomer or elastomeric article using a solvent in a non-supercritical state to substantially remove  
10 impurities therefrom and thereafter subjecting the elastomer or elastomeric article to a further solvent extraction step using a supercritical fluid or a mixture of supercritical fluids in order to remove or substantially reduce the concentration of the residue of extracting solvent remaining in the elastomer or  
15 elastomeric article after the first solvent extraction process.

2. A method as claimed in claim 1 wherein the  
20 supercritical fluid is carbon dioxide (CO<sub>2</sub>).

3. A method as claimed in claim 1 or claim 2 wherein the solvent used in the first extraction  
process is one or comprises one which is too toxic to be employed in a conventional extraction of impurities  
25 but whose residues are reduced to a level of acceptable toxicity by the supercritical fluid extraction step of this method.

4. A method as claimed in claim 3 wherein the  
30 solvent used in the first extraction process is a ketone, for example acetone.

5. A method as claimed in any one of claims 1  
to 3 wherein the solvent used in the first extraction  
35 is an aliphatic alcohol.

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6. A method as claimed in any one of claims 1 to 3 wherein the solvent used in the first extraction is a partially or fully halogenated alkane.

5        7. A method as claimed in any one of claims 1 to 3 wherein the solvent used in the first extraction is a polyhydric alkane.

10       8. A method of cleaning or purifying elastomers and elastomeric articles which are intended for medical or pharmaceutical use and which have already been subjected to a solvent extraction process using a solvent in a non-supercritical state to remove  
15       impurities therefrom, which method comprises removing or substantially reducing the solvent residue from the solvent extraction process remaining in the elastomer or elastomeric article by extraction with a  
20       supercritical fluid or a mixture of supercritical fluids.

25       9. Use of a supercritical fluid or a mixture of supercritical fluids to remove or substantially reduce the concentration of the residue of a solvent in an elastomer or elastomeric article intended for medical  
30       or pharmaceutical use which solvent has been used in a non-supercritical state to extract impurities from said elastomer or elastomeric article.

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## INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 C08J7/02 C08C3/02 B01D11/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C08J C08C B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 417 768 A (SMITH JR CHARLES W ET AL) 23 May 1995 see abstract; claims see column 4, line 38 - column 6, line 11 ---	1-9
Y	US 5 481 058 A (BLACKWELL JOHN A ET AL) 2 January 1996 see abstract; claims; example 9 see column 3, line 28 - column 4, line 49 ---	1-9
A	WO 94 13733 A (VALOIS SA ;TCHEREVATCHENKOFF ANDRE (FR); PERRE CHRISTIAN (FR)) 23 June 1994 see abstract; claims; examples -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5417768 A	23-05-95	US 5509431 A	23-04-96
US 5481058 A	02-01-96	CA 2180676 A	13-07-95
		EP 0738288 A	23-10-96
		WO 9518834 A	13-07-95
WO 9413733 A	23-06-94	FR 2699544 A	24-06-94
		DE 69309103 D	24-04-97
		EP 0674679 A	04-10-95
		JP 8506046 T	02-07-96